MEMORANDUM

DATE: June 3, 1999

FROM: Mark Thornton, M.D., M.P.H., Ph.D.
IID Branch / DCTDA / OTRR

SUBJECT: Clinical Review of Response to Complete Response Letter for BLA Supplement 98-0207 Roferon-A (interferon alfa-2a) in the treatment of hepatitis C

THROUGH: William Schwieterman, M.D.
Branch Chief, IID / DCTDA / OTRR

TO: Karen Weiss, M.D.
Director, DCTDA / OTRR

PRODUCT LICENSE SUPPLEMENT

REFERENCE NUMBER: 98-0207

ORIGINAL APPLICATION RECEIPT DATE: 2-17-98

COMPLETE RESPONSE LETTER ISSUE DATE: 1-19-99

SPONSOR RESPONSE TO COMPLETE RESPONSE LETTER DATE: 2-1-99

PRODUCT: Roferon-A (interferon alfa-2a)

SPONSOR: Hoffman La-Roche, Inc.

INDICATION: Hepatitis C

CLINICAL REVIEWER: Dr. Mark Thornton

Clinical Review of BLA 98-0207 Roferon 6-3 regimen

Background

Hoffman-LaRoche submitted a BLA (98-0207) supplement for Roferon-A on February 17, 1998 to expand their label to contain new Roferon dosing information following clinical trials performed in the early and mid 1990's.

Dr. Ilana Fogelman performed a review of the BLA in 1998. There were mid-cycle meetings and a decision to issue a Complete Response letter. The letter was issued on January 19, 1999 and a response from Roche was received February 1, 1999.

This review did not attempt to repeat the effort by Dr. Fogelman, but instead focused on the issues in the CR letter. Dr. Fogelman's review is found as an appendix to this review.

There were three questions posed in the CR letter with various parts to each. This review will consist of a restatement of the question posed by the Agency, a summary of the response by Roche, comments about the value and appropriateness of the response, and whether our questions were sufficiently answered.

Question 1. In order to characterize the safety profile of high dose Roferon®-A, we recommend that you review the 12 weeks safety data generated in prior randomized controlled studies in which 6 MIU three times a week of Roferon®-A was compared to the labeled regimen of 3 MIU three times a week. Please provide us with tables indicating the overall incidence, as well as the incidence of serious adverse events , by body system. Please indicate the number of patients that experienced a dose modification or withdrew from the study due to an adverse event during the initial 12 weeks of the randomized studies you review. Please provide us with a similar list of dose modification and patient withdrawls during the 12 week period in your current study submitted with this BLA supplement.

Response 1. Prior to study NV14524 (the subject of the current submission), two registration studies were conducted by the sponsor in which 3 MIU administered three times a week (tiw) was directly compared to the administration of 6 MIU tiw. Both studies were conducted in parallel within the United States between 1990 and 1992. These studies are identified as N3414 and N3505. The Final Study Reports for both studies were submitted in the original BLA supplement for the hepatitis C indication (Submission 94-0782) and are identified as Roche report B-154'511 and B-154'512, respectively. The current supplement focuses on study NV14524 (report N-139203), which looks at "induction" dosing with 6 MIU for 3 months followed by either 3 or 9 months of treatment with 3 MIU. **Table 1.1** summarized the study characteristics of these three studies, N3414, N3505, and NV14524, which were used in responding to this request.

Question #1 Reviewer's assessment

Methods

The information cited above by the sponsor was reviewed. To optimally assess the adverse events elicited by the 6 MIU vs. 3 MIU doses of Repheron, a subset was chosen of the data submitted by the sponsor. Specifically, it was thought that the best comparison to answer the question posed would be to compare incidences of adverse events between Trials 3414 and 3505 (where 3 MIU tiw x 24 weeks was employed) with Trial 14524 (where the 6 MIU tiw x 24 week subset was presented by the sponsor.)

In addition, to acknowledge the problems inherent in comparing clinical trials performed with different protocols at different times, it was thought that only strong signals of differences in adverse events between the regimens would be relevant for making decisions impacting the labeling of the product. Accordingly, the tables below represent those adverse events where there was either a ≥ 5 or 10 % difference between one regimen and the other.

Finally, the format described above was presented for both the adverse events judged to be possibly or probably related to treatment and for those all adverse events collected regardless of relatedness. The former subset is considered to be more precise medically, since medical judgement was involved in decisions about relatedness. However, the latter group is considered to be least effected by bias, albeit with the potential to be less specific. Ideally, the trends would be the same in both sets of data.

ADVERSE EVENTS POSSIBLY/PROBABLY RELATED TO TREATMENT

10% OR GREATER DIFFERENCE

Body System	Adverse Event	Trial 3414 3MIU n=94 % of total	Trial 3505 3MIU n=109 % of total	Trial 14524 6MIU n=212 % of total
Body as a whole	Chills	16	28	65
	Fever	27	28	54
	Flu-like symptoms	31	30	2
Musculo-skeletal	Total system	41	44	66
	Myalgia	30	27	47
	Arthralgia	9	14	38
Gastrointestinal	Anorexia/appetite decreased	0	0	26
	Anorexia	11	16	0
Psychiatric	Total system	35	20	45

5% OR GREATER DIFFERENCE

Body as a whole	Chills	16	28	65
	Fever	27	28	54
	Flu-like symptoms	31	30	2
CNS/PNS	Headache	51	41	60
Musculo-skeletal	Total system	41	44	66
	Myalgia	30	27	47
	Arthralgia	9	14	38
Psychiatric	Total system	35	20	45
	Depression	18	11	23
	Irritability	15	12	22
	Concentration impaired	6	2	12
Gastrointestinal	Anorexia/appetite decreased	0	0	26
	Anorexia	11	16	0
Psychiatric	Total system	35	20	45
Eye/Vision	Total system	3	1	8

ALL ADVERSE EVENTS, REGARDLESS OF RELATEDNESS

10% OR GREATER DIFFERENCE

	Adverse Event	Trial 3414 3MIU n=94 % of total	Trial 3505 3MIU n=109 % of total	Trial 14524 6MIU n=212 % of total
Body as a whole	Chills	18	28	66
	Fever	28	30	55
	Flu-like symptoms	36	34	2
Musculo-skeletal	Total system	56	50	71
	Myalgia	32	27	49
	Arthralgia	10	14	41
Gastrointestinal	Anorexia/appetite decreased	0	0	26
	Anorexia	12	17	0

5% OR GREATER DIFFERENCE

	Adverse Event	Trial 3414 3MIU n=94 % of total	Trial 3505 3MIU n=109 % of total	Trial 14524 6MIU n=212 % of total
Body as a whole	Chills	18	28	66
	Fever	28	30	55
	Flu-like symptoms	36	34	2
CNS/PNS	Headache	56	46	64
	Taste alteration	5	3	10
	Forgetfulness	0	0	7
Musculo-skeletal	Total system	56	50	71
	Myalgia	32	27	49
	Arthralgia	10	14	41
Gastrointestinal	Anorexia/appetite decreased	0	0	26
	Anorexia	12	17	0
	Throat sore	4	6	11
	Abdominal discomfort	0	0	5
Psychiatric	Total system	38	23	47
	Depression	18	13	25
	Irritability	15	12	23
	Concentration impaired	6	3	12
Resistance Mechanism	Total system	9	8	14
Eye/Vision	Total system	6	2	12

Question #1 Reviewer Comments:

It appears that the higher doses of Roferon, given in the same t.i.w. regimen as the lower dose, elicit higher incidences of flu-like symptoms, including chills, fever, myalgia, arthralgia and anorexia. There is also a trend towards higher incidences of psychiatric symptoms of depression, irritability, impaired concentration and anorexia. The findings of differences in incidences between the regimens for "Resistance Mechanism" and "Eye/Vision" are probably either a non-specific finding or represent multiplicity within the database due to the number of adverse events assessed.

Question 2. There was a drop in sustained ALT responses from 15% to 10% beyond the 6-month end-of-treatment timepoint in patients in the 24 week treatment arm. Please provide us with a list of these patients, indicating whether they failed interferon therapy, or withdrew from this study because of adverse events or other reasons. Please include the values and dates of their ALT and viral load measurements beyond the 6-month-end of treatment timepoint.

Response 2. In study NV14524, patients randomized to receive 48 weeks of treatment were to have 24 weeks of untreated follow-up. Patients randomized to receive 24 weeks of treatment would receive 48 weeks of follow-up instead of the traditional 24 weeks, to give a common overall observation period of 72 weeks for both arms of the study. It is the sponsor's understanding that it is the disposition of patients during the second 24 weeks of observation (study weeks 48-72) that is of interest.

Ten of thirty-two patients who had a sustained ALT response 24 weeks after stopping treatment (study week 48) did not have a sustained response at the end of a 48 week follow-up (study week 72). **Table 2.1** listed these ten patients and provided the date of last observation and information on disposition of patients between weeks 48 and 72. It also provided information on the ALT and viral load response status of these patients at the time of last observation. Data supporting the disposition of patients can be found in the BLA supplement in the study report for NV14524, report N-139203 (Module I, Appendix 5).

Of these ten patients, six decided not to complete the second 24 weeks of follow-up ("lost to follow-up") One patient was determined to be a treatment failure during the second 24 weeks of follow-up. Three additional patients are listed as "completed study." These patients did not meet the criteria for discontinuation (complete loss of response by both ALT and PCR), but also did not meet the definition of complete responders by ALT (two consectutive normal ALT values) at the end of the second 24 weeks. The viral load response for these ten patients confirms the ALT data when available at the same timepoint.

Question #2 Reviewer Comments:

Based on the information provided, it appears that the drop in SR from 15 to 10% is mostly due to an inability to account for the responding patients. Since the analysis is conservative and assumes these patients to be treatment failures, it may not represent the true percentage that maintain a response to Roferon. On the other hand, three of the ten patients did begin to show some indications of failing therapy, since either the ALT or the viral endpoint failed to sustain the response seen at the initial end of follow-up. One person of the 10 was a bona fide treatment failure during the 48-72 week follow-up period. No patients withdrew due to adverse events.

The implications of these findings are minimal for labeling purposes, since the end of follow-up time of 24 weeks in the standard time for relative comparisons of competing interferons' effectiveness. However, medically, it is not a good sign that patients who have established a SR for 6 months after end of treatment begin to show signs of returning to an infectious and diseased condition.

Question 3. Forty-nine patients in the 24-week arm continued to receive Roferon®-A beyond 24 weeks. Please explain this protocol violation. In addition, please provide us with the list of such patients indicating whether these patients had a normalization of their ALT and viral load responses

Response 3. For this study, the treatment period is defined as 168 days (24 weeks times 7 days). It would be expected that the patient would have 72 injection days within this treatment period

Test medication for this study was dispensed to the patient at monthly clinic visits in a box containing 15 single use vials (3 per week for four weeks of tiw dosing, plus 3 extra vials). These extra vials could be used during the treatment period to allow some flexibility in scheduling patient visits, since it not always convenient for the patient to return to the clinic exactly every 28 days for a check-up and to receive a new supply of test medication.

Please Explain this Protocol Violation

Table 3.1 summarized the number of injections received by the 49 patients whose treatment period extended beyond 24 weeks. **Table 3.2** summarized for the 49 patients the number of days beyond 168 days in their treatment period.

Table 3.1 Total Number of Injections Given by the Forty-nine Patients Who Exceeded the 168 Day Treatment Period

Additional Weeks of Test Medication	Number of Injections*	Number (%) of Patients Taking Injections
	< 72	8 (16.3)
	72	8 (16..3)
1	73 - 75	19 (38.9)
2	76 - 78	8 (16.3)
3	79 - 81	5 (10.2)
≥ 3	83	1 (2.0)

. * The number of doses (injections) is listed, not the number of potential injection days, since some patients skipped their injections for a variety of reasons

Table 3.2. Total Number (%)of Days of Treatment Period for the Forty-nine Patients who Exceeded the 168 Day Treatment Period

Treatment Period	Number (%) of Patients
169 - 175	33 (67.3)
176 - 182	9 (18.4)
183 - 189	4 (8.2)
190 - 196	1 (2.0)
197 - 201	2 (4.1)

Although 49 patients had a treatment period exceeding 168 days, the majority (33/49, 67%) extended treatment by no more than one week, and 42/49 (86%) extended treatment by no more than two weeks. Eight patients (16%) received fewer than 72 doses and eight (16%) received the required 72 doses, even though their treatment period was extended. Another nineteen (39%) received between one and three additional doses beyond the prescribed 72 doses.

Although a treatment extension beyond 72 doses or 168 days is a protocol violation, the sponsor believes that the extension occurred as a consequence of scheduling patient clinic visits, rather than as intentional violation by the patient or investigator. Over a period of 24 weeks, if visits had to be adjusted even by a few days, the patient would need to use one or more of the extra vials provided in the monthly supply of medicine in order to keep on a thrice weekly dosing schedule. The more visits that had to be adjusted, the more the chance that additional vials would be consumed and the treatment period would become extended.

Table 3.3 listed the 49 patients who had a treatment period that extended beyond 168 days. This table listed ALT and viral load responses (PCR) at weeks 12, 24, 48 and 72. In this table, CR denoted complete response (normalization of ALT or undetectable HCV RNA by PCR technology) and NR denoted no complete response.

Question #3 Reviewer Comments:

The explanations offered by the sponsor for the reasons for treatment beyond 24 weeks seem reasonable in the contexxt of how the clinical trial was performed. Of the 49 patients who received more than 24 weeks of therapy, 86% stopped within 2 weeks after the cut-off date.

Regarding ALT and viral responses in the 49 patients, 9/49 (18.4%) had sustained response to ALT and 6/49 (12.2%) had a sustained virologic response. These values are slightly higher than the total group response for ALT (15%) and slightly lower for the total group virologic response (13%), so it is difficult to assign any significance to the receipt of Roferon beyond the 24 weeks of protocol-defined treatment. Therefore, it would seem appropriate to allow these patients to remain in summary statements about the efficacy of the 24 week Roferon regimen.

Overall Recommendations:

The review performed by Dr. Fogelman served as the basis for the CR letter issued in January, 1999. In that review, the recommendations called for allowing reference in the label to these studies depending "on the demonstration by the sponsor based on previous controlled studies that 12 weeks of high dose Roferon-alpha is not associated with unacceptable toxicities relatively to the labeled 3 MIU regimen". Although there does appear to be some increased incidences in selective adverse events as a result of the higher Roferon doses, there is also the benefit of the improved SR rate from the 6 to 3 MIU regimen. The toxicities are not unacceptable [redacted]

Submitted by:

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6/3/99

Date